REMARKS/ARGUMENTS

After entry of the above amendments, Claims 531-542, 547-548, 551-552, 555, 558, 560, 569-576 and 581-582 are currently pending, Claims 531, 551 and 581 are amended hereby and new Claim 582 has been added. Support for these amendments and for new Claim 582 can be found in the specification, drawings and claims as filed. No new matter has been added by these amendments or by the addition of new Claim 582. Claims 531-542, 547, 548, 550-552, 555, 558, 560, 569-576 and 581 have been rejected by the Examiner in an Office Action dated December 26, 2007. This Amendment and Response constitutes Applicants' reply to that Office Action. As set forth more fully below, reconsideration and withdrawal of all of the Examiner's rejections is respectfully requested.

A. Rejection Under 35 U.S.C. § 112

The Examiner has rejected Claims 531-542, 547, 548, 550-552, 555, 558, 560, 569-576 and 581 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims. Applicants traverse this rejection for the reasons already of record and for the following additional reasons.

The claims have now been further narrowed by the present amendments to specify that P_2 comprises a Cu(I) binding site. Thus, the peptides covered by presently pending claims comprise a P_1 sequence that can bind a transition metal ion, particularly Cu (II), and a P_2 sequence that can bind a Cu(I) ion. Support for these amendments can be found, for example, at page 14, line 25 through page 15, line 20 and page 17, line 21 through page 18, line 21, of the present specification.

The testing of several such peptides[1] is described in the Declaration of Dr. David Bar-Or ("Bar-Or Declaration"), submitted with Applicant's April 20, 2006 response. The peptides were tested in a variety of assays which demonstrated their ability to bind copper and inhibit angiogenesis, and the Bar-Or Declaration provides in excess of 20 working examples which demonstrate the efficacy of the presently claimed metal-binding peptides having two metal-binding sites. Indeed, all of the peptides showed efficacy in each of the various assays in which they were tested, and they were generally the most effective of the peptides tested. Further, the peptides, which comprise a P_1 sequence that can bind a transition metal ion, particularly Cu (II), and a P_2 sequence that can bind a Cu(I) ion, were found to have a very high copper-binding affinity, much higher than that of peptides containing only the P_1 metal-binding site. See paragraph 6 and Exhibit D of the Bar-Or Declaration. It is submitted that other peptides having these two types of copper-binding sites would be expected to also have very high copper-binding affinity and that such high-affinity binding of copper would be expected to lead to inhibition of angiogenesis, since copper is required for angiogenesis (see, *e.g.,* page 39, lines 24-27, of the present specification).

Applicants submit that the data presented in the Bar-Or Declaration confirm and establish that the guidance presented in the specification is sufficient to enable one of skill in the art to make and use the invention as currently claimed without undue experimentation. It should be noted that Applicants need not describe all actual embodiments of their invention. See MPEP § 2164.02. The data in the Bar-Or Declaration in combination with the disclosure in the specification demonstrate that peptides coming within the scope of the present claims are effective in inhibiting angiogenesis.

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[1] Among the peptides that were tested are:
Asp Ala His Gly Met Thr Cys Ala Arg Cys;
Asp Ala His Gly Met Thr Cys Ala Asn Cys;
His Ala His Gly Met Thr Cys Ala Asn Cys;
Asp Ala His Lys Gly Met Thr Cys Ala Asn Cys; and
Asp Ala His Gly γGlu Cys Gly.

As noted above, Applicants have now provided in excess of 20 working examples and, therefore, submit that there are certainly sufficient working examples of record to support a finding of enablement of the currently pending claims.

The Examiner contends that the art of inhibiting angiogenesis using metal chelating agents was unpredictable at the time of the filing of the present application. However, all of the Examiner's remarks are concerned with compounds that comprise only one metal-binding site, not two metal-binding sites, as provided by the peptides covered by the currently pending claims.

First, the Examiner relies on Lane *et al.* as teaching that the peptide Lys Gly His Lys stimulates angiogenesis and contends that this is evidence of unpredictability. However, this peptide contains only one metal-binding site (a Cu(II)-binding site; *see, e.g.*, the Abstract of Lane *et al.*) and does not come within the scope of the present claims. Further, contrary to the Examiner's contention, Xaa_2 in Applicants' present claims is not defined to include glycine.

Second, the Examiner states that the fact that Tyr Lys His, Ser Ser His, D-Phe Gly His and Asp Ala His Arg Arg Arg Arg Arg Arg do not inhibit proliferation of endothelial cells in Applicants' assays is evidence that these peptides do not inhibit angiogenesis and, therefore, is evidence of unpredictability. However, proliferation is only one of the three steps of angiogenesis (see Bar-Or Declaration, paragraph 5, and Applicants' response filed April 20, 2006, paragraph bridging pages 13-14), so lack of inhibition of proliferation does not demonstrate lack of inhibition of angiogenesis. In fact, these peptides did inhibit release of IL-8, a potent promoter of angiogenesis (see paragraph 4 and Exhibit B of the Bar-Or Declaration, and Applicants' response filed April 20, 2006, second full paragraph on page 13).[2] More important, none of these peptides comes within the scope of the present claims as they contain only one metal-binding site.

For all of the foregoing reasons, Applicants request the Examiner's rejection be withdrawn.

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[2] Ser Ser His, Phe Gly His and Asp Ala His Arg Arg Arg Arg Arg Arg were tested in this assay and were found to strongly inhibit release of IL-8. Tyr Lys His was not tested in this assay.

CONCLUSION

Based upon the foregoing, Applicants believe that all of the pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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